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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,395	11/20/2000	Stephen W. Fesik	6752.US.01	8628

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,395	FESIK ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14* is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-14) in Paper No. 9, received December 23, 2002 is acknowledged.

2. Claims 1-14 are pending.

Claims 15-18 have been cancelled.

Claims 1-14 are examined on the merits.

Drawings

3. The drawings are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2 and 4-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2 and 4-13 broadly claim a mutant protein derived from a wild-type human Bcl-2 protein wherein a sequence of amino acid residues comprising a flexible loop from said wild-type human Bcl-2 protein is replaced with a replacement amino acid sequence comprising at least two acidic amino acids, wherein the replacement amino acid sequence comprises a sequence of at least 16 to about 50 amino acid residues. Additionally, the said mutant protein have a flexible loop comprising amino acids 35-91 and have an isoelectric point from 4.5 to about 6. The written description in this instant case only sets forth SEQ ID NO:2 comprising replacement amino acid sequence, SEQ ID NO: 1 consisting of 16 amino acids, therefore the written description is not commensurate in scope with the claims drawn to the said broadly claimed mutant protein.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or

simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Applicants pointedly express support for a human Bcl-2 mutant polypeptide within the bridging paragraph of pages 7 and 8 of the specification. Applicants also assert "[t]he mutant Bcl-2 proteins of the present invention can contain from about 150 to about 180 amino acid residues." However, the specification only supports one mutant polypeptide consisting of 166 amino acids defined as SEQ ID NO: 2. There is no disclosure, beyond the mere mention of possible other mutants is made in the specification. This is insufficient to support the generic claims as provided by the

Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

6. Claims 1, 2 and 4-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 2 and 4-13 broadly claim a mutant protein derived from a wild-type human Bcl-2 protein wherein a sequence of amino acid residues comprising a flexible loop from said wild-type human Bcl-2 protein is replaced with a replacement amino acid sequence comprising at least two acidic amino acids, wherein the replacement amino acid sequence comprises a sequence of at least 16 to about 50 amino acid residues. Additionally, the said mutant protein have a flexible loop comprising amino acids 35-91 and have an isoelectric point from 4.5 to about 6.

The specification while being enabling for the polypeptide having the amino acid sequence of SEQ ID NO:2 comprising SEQ ID NO: 1, does not reasonably provide enablement for the myriad of variant polypeptides embraced by the broad claims. There is no guidance as to how to make these divergent sequences. The mutant proteins derived from the wild-type human Bcl-2 protein consisting of undefined replacement amino acid sequences of about 4 to 50 amino acid residues may possess function that is not commensurate with the functions of the native protein. These variant proteins containing at least a portion of a flexible loop from human Bcl-x_L may not

maintain the activities proposed in the specification. It would seem that specific function(s) would be required to make the encoded protein useful for the applications disclosed in the specification, such as screening assays to identify compounds useful as anti-cancer agents for treating disorders associated with cancer and other diseases caused by the impairment of the apoptotic process. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid or acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful. The true fact of the state of the art in peptide chemistry is expressed succinctly in the accompanying Lazar article (Molecular and Cellular Biology 8(3): 1247-1252, March 1988). This article presents data that substantiates the fact that the introduction of mutations in an amino acid sequence will yield products with different biological activity from the wild type protein.

From the discussion above, it is clear that the predictability of changes to the amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed polypeptides in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which must be made in the amino acid sequence of the wild-type human Bcl-2 protein, which results in a

mutant protein other than SEQ ID NO: 2 and retaining anti-apoptotic inhibitor function is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation "flexible loop" in claims 1, 2 and 9 is vague and indefinite. It follows that the loop is essential to the wild-type and mutant human Bcl-2 proteins, however it is not clear what defines the loop, i.e. amino acid residues, structural juxtaposition. Applicants are requested to further clarify the flexible loop.

b. Claim 2 is vague and indefinite in the recitation "at least a portion of a flexible loop". It is not clear how many amino acids coding for the flexible loop would be necessary to maintain structure and function. Accordingly, the metes and bounds are unclear.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,214,986 (filing date June 2, 1999). Sequence 2 in columns 51 and 53 of the patent discloses a human mutant protein derived from a wild-type human Bcl-2, see attached database sheet at the end of the patent. The disclosed mutant protein contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1, see highlighted section of attached database sheet.

It is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

11. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent number 5,646,008 (July 8, 1997). Sequence 7 in columns 53 and 54 of the patent discloses a human mutant protein derived from a wild-type human Bcl-2, see attached database sheet at end of the patent. The disclosed mutant protein contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1, see highlighted section of attached database sheet.

It is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

12. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Boise et al. (Cell 74: 597-608, August 27, 1993/ IDS reference C3). Figure 3 on page 599 of Boise discloses a human bcl-x_L mutant protein, see attached database sheet. The disclosed mutant protein contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop, see attached database sheet. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1, see attached database sheet.

It is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

13. Claims 1-8 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Muchmore et al. (Nature 381:335-341, May 23, 1996/ IDS reference C7. The first listed sequence on page 337 of Muchmore discloses a human bcl-x_L mutant protein, see attached database sheet. The disclosed mutant protein contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop, see attached database sheet. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1, see attached database sheet.

It is reasonable to conclude the anticipatory mutant protein would have an isoelectric point lower than that of wild-type Bcl-2, wherein it is from 4.5 to about 6.0.

2.

14. Claims 9 and 14 are free of the art.

Allowable Subject Matter

15. Claim 14 is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
March 23, 2003